REMARKS

Status of Claims and Amendment

This Amendment, filed in reply to the Office Action dated May 13, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1 and 25-27 have been amended. Claim 2 has been canceled without prejudice. Claim 24 was previously canceled without prejudice or disclaimer. Claims 7-23 and 28-30 are withdrawn from consideration. Claims 1, 3-23, and 25-30 are all the claims pending in this application. Claims 1-6 and 25-27 are rejected.

Claim 1 has been amended to incorporate the limitations of claim 2.

Claims 25-27 have been amended to correct a clerical error. Support for the amendment to claims 25-27 may be found throughout the specification, for instance, at page 9, line 12 to page 10, line 2. One of ordinary skill in the art would understand from reading the disclosure that the desired protein amount is determined from the protein content expressed in the eggs.

No new matter is added.

Withdrawn Rejections - Obviousness Type Double Patenting

Applicants thank the Examiner for withdrawing the rejection of claims 1-6 and 25-27 for obviousness-type double patenting as being unpatentable over claims 1, 41, 44-47 and 49-56 of copending U.S. Patent Application No.: 10/523,191.

Claims 25-27 are Patentable Under 35 U.S.C. § 102(e)

Claims 25-27 remain rejected under 35 U.S.C. § 102(e) as being anticipated by Ransohoff *et al.* (U.S. Patent Application Publication 2003/0176660), for the reasons set forth on page 5 of the Office Action mailed March 19, 2008 and pages 3-4 of the Office Action mailed October 3, 2008.

Applicants' arguments that claim 1 is not directed to the offspring from G0 transgenic chimeras that do not contain the transgene since a G1 transgenic bird involves germline transduction of the transgene and would produce eggs containing the transgene and the MMLV-derived vector sequences, was not found to be persuasive. The Office Action appears to maintain the rejection on the basis that the process steps of claim 1 does not necessarily result in germline transduction and cannot result in the production of a true transgenic bird or eggs that contain the transgene nor the MMLV-derived vector sequences since the steps involve mating a G0 transgenic chimeric bird with any other G0 transgenic chimeric bird or a with a wild type bird.

Specifically, the Office Action states that by definition, a G0 chimeric bird carries the transgene in only some of its somatic cells and is not capable of germline transmission of the transgene so that crossing a chimeric bird with a wild type bird or a non-related chimeric bird, would further dilute the transgene and cannot result in the production of a true transgenic bird. Therefore, the Office Action asserts that the resulting product of claim 1 is correctly interpreted and all of the words in claim 1 have been considered in determining whether the claimed product is a chimeric or a transgenic chimeric chicken.

Applicants disagree for at least the following reasons.

As previously argued, the recitation of a "***transgenic*** bird ... which is obtained as a G1 ***transgenic*** bird or an offspring thereof" in claim 1 cannot be ignored, and construed to be directed to nontransgenic birds, i.e., the offspring from G0 chimeras that do not contain the transgene. In this regard, the Office Action's assertions that the G1 bird in claim 1 is a chimeric bird in view of the process steps recited is incorrect because the difference between a chimeric and transgenic animal is distinct. A chimera is an animal that has two or more different populations of genetically distinct cells. In contrast, all cells including germline cells of the claimed G1 birds contain the same genetic information. Therefore, the claimed G1 bird is not chimeric.

Further, the Office Action's statement that "by definition, a G0 chimeric bird carries the transgene in only some of its somatic cells and is not capable of germline transmission of the transgene", is also incorrect. As discussed above, a chimera is an animal with two or more different populations of genetically distinct cells. In this respect, genetically distinct cells (e.g., cells that contain an exogenous antibody gene as in the present invention) in a chimera may be somatic or germline. When the cells with the exogenous antibody gene are germline cells, at least half of the G1 animals have exogenous antibody gene in all of their cells. In the present invention, the claimed G1 transgenic bird would be produced from a G0 transgenic chimeric bird, as recited, with a transgene in its germline cells. Accordingly, as long as the G0 bird has an exogenous antibody gene in its germline cells, the claimed G1 animal is never a chimera.

Thus, because the process steps of claim 1 impart structural differences between the claimed product in comparison to the product of Ransohoff, Ransohoff does not anticipate the claimed invention.

Withdrawal of the rejection under 35 U.S.C. § 102(e) is respectfully requested.

Claims 1 and 3-6 are Patentable Under 35 U.S.C. § 103(a)

Claims 1-6 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Sang *et al.* (U.S. Patent Application Publication 2005/0273872), as evidenced by Kamachi *et al.* (Development 125:2521-2532; 1998), in view of Rapp, J. (U.S. Patent Publication No. 2002/0108132, effective filing date Feb. 2, 2001), for the reasons of record. For brevity, these reasons are not reiterated herein.

Applicants' arguments that Sang differs from the claimed invention because Sang discloses inoculation of chicken embryos at any of stages X-XIII, *i.e.*, blastodermic stages, while the claimed transgenic bird of the present invention is produced by microinjection of a MMLV-derived vector "at a stage except for and after the blastodermic stage just after egg laying," *i.e.*, just after egg laying and after the blastodermic stage which imparts unexpectedly distinct and nonobvious structural characteristics, was not found to be persuasive. The Office Action asserts that, as evidenced by Kamachi, stage XIII chick embryos include the gastrula stage, *i.e.*, up to and including 48 hours and the instant claims do not require the production of proteins of a specified concentration. Moreover, the Office Action asserts that any differences between the claimed invention and the prior art would be expected to result in some differences in properties, but the properties would not differ to an extent that the difference is really unexpected. Also, the

Office Action asserts that Applicants recognition of enhanced transgene expression would have flown naturally from the process of making a transgenic chicken according to the stage XIII embryos.

Also, Applicants' arguments that Sang explicitly teaches away from using a MMLV-derived vector during development and that the Office improperly relied upon subsequent publications to support an obviousness inquiry rather than the art recognized knowledge in the art at the time the invention was made that one of ordinary skill in the art would have considered the MMLV-derived vectors to result in transgene silencing in avians because regulation of gene expression during early embryogenesis is highly conserved amongst vertebrates, was not found to be persuasive. The Office Action appears to rely on the argument that the gene silencing is during mouse embryogenesis, and not extendible to avians, and that arguments regarding the reliance on subsequent publications are arguments of counsel that cannot take the place of evidence in the record.

Applicants respectfully disagree for at least the following reasons.

First, the Office Action has improperly ignored the recitation in claim 1 that the microinjection is "at a stage except for and after the blastodermic stage just after egg laying". In this respect, the Office Action's contention that lentiviral vectors are infected into the chicken embryos at developmental stages X-XIII in Sang, and Stage XIII chicken embryos include the gastrula stage, up to and including 48 hours, as evidenced by Kamachi, is incorrect. The developmental stages of chicken embryos in Sang and Kamachi are different from each other. In Kamachi, the developmental stages are defined according to Hamburger and Hamilton (1951)

(see page 2524, 2nd paragraph, right column of Kamachi), and the stages are counted based on the hours after egg incubation (see left column of SUMMARY of Kamachi). In contrast, the developmental stages in Sang are defined according to Eyal-Giladi & Kochav (1976) (see [0064] of Sang) which teaches that the "[f]ourteen developmental stages preceding Hamburger and Hamilton's stage 2 have been studied from live material..." (see Abstract of Eyal-Giladi). Accordingly, since Hamburger and Hamilton's stage 2 is 7 hours after the start of incubation, virus infection at stages of X-XIII in Sang means that Sang infects viruses 7 hours after the start of incubation, at the latest. Therefore, the developmental stages described in Sang are distinct from Kamachi.

Furthermore, as acknowledged by the Office Action, Sang discloses inoculation of chicken embryos at any of stages X-XIII, *i.e.*, blastodermic stages (see page 6 of Office Action mailed October 3, 2008), and Sang does not teach the production of transgenic chimeric chicken using a retroviral vector derived from MMLV (see page 6 of Office Action mailed October 3, 2008).

Moreover, in contrast to Sang, the time period of virus infection to the embryo is at least 24 hours after the start of incubation, as presently claimed. As discussed in the present specification (see paragraphs [0064] and [0103]), the time of placing eggs in an incubation condition is taken as zero hour. Since Sang explicitly teaches virus infection is performed 7 hours after the start of the incubation at the latest, one of ordinary skill in the art would not have been motivated to try to infect viruses at least 24 hours after the start of incubation.

Second, Applicants assert that the Office Action not met the ***initial*** burden of establishing a *prima facie* case of obviousness. In addition to the foregoing and previous arguments, the Office Action acknowledges that, "Sang et al. state that it is essential that *any* viral vector used for *production of transgenic birds* does not exhibit gene silencing [emphasis added]". Applicants remind the Office that all relevant teachings must be considered in determining the obviousness of the claimed invention. M.P.E.P. 2144.08. In the present case, the art *as a whole*at the time the invention was made, as evidenced by Sang, teaches away from the presently claimed invention because Sang *explicitly* teaches that the use of a delivery vector derived from MMLV during development leads to gene silencing, and "very low expression of the transgene," and that "it is therefore essential that any viral vector used for production of transgenic birds does not exhibit gene silencing" (see paragraph [0016] of Sang). Further, when the prior art teaches away from the claimed solution, the Board of Patent Appeals and Interferences has interpreted the ruling in *KSR* to mean that obviousness cannot be proven merely by showing that a known element could have been modified by routine experimentation or solely on the expectation of success. *Ex parte Whalen* (BPAI 2008).[2] "[I]t must be shown that those of ordinary skill in the art would have had some apparent reason to modify the [art] in a way that would result in the claimed [invention]." Id.

[2] The Supreme Court stated that "because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement...Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR* at 1740-41.

In addition, the Office has failed to provide any evidence to support the contention that one of ordinary skill in the art would have somehow been motivated to arrive at the claimed invention, especially based upon the teachings of Sang discussed above. Rather, the Office continues to improperly rely upon "the body of subsequent publications with regard to using Moloney murine leukemia virus as an expression vector in chimeric or transgenic birds" (see page 6 of present Office Action). As previously argued, such reliance is improper because an obviousness inquiry is determined based on the knowledge of those of ordinary skill in the art *at the time the invention was made*. M.P.E.P. § 2141.01. In fact, the teachings of Sang is evidentiary support for Applicants' position that, at the time of the invention, the art recognized that regulation of gene expression, including gene silencing, during early embryogenesis is highly conserved amongst vertebrates, and as such, one of ordinary skill in the art, at the time of the invention, would have considered that MMLV-derived vectors would result in transgene silencing in avians. Thus, the Office Action has not fulfilled the ***initial burden*** of establishing a *prima facie* case of obviousness, especially in view of the knowledge available in the art at the time the invention was made.

Furthermore, Applicants note that unexpected results is evidence of the nonobviousness of the claimed invention. As previously argued, the claimed process steps result in a transgenic bird and egg thereof, with unexpectedly superior transgene expression in comparison to the transgenic birds of Sang and Rapp, because of the microinjection of a MMLV at the claimed specific developmental stage.

With regard to the expression amount of the exogenous proteins, Rapp shows in Figures 1-3 that the amount of the antibody expression is not more than 50 ng/ml. Sang shows in Fig. 4b that the amount of exogenous protein expression is not more than 100pg/microgram. Based on the disclosures in Sang and Rapp, one of ordinary skill in the art would not have had a reasonable expectation of success of obtaining as much as, for example, 1.5~1.6 mg/ml of antibody expressed in the blood, and as much as 0.33~0.57 mg/ml expressed in egg yellow and egg white, as achieved by the present invention (see Tables 1-4). Further, as demonstrated in Tables 2 and 3, the presently claimed invention results in unexpected inhibition of transgene silencing in future generations, such as G2 transgenic offspring. In view of the unexpectedly superior properties for transgene expression imparted by the presently claimed invention, Rapp and Sang, alone or in combination, does not render the claimed invention obvious.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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